REMARKS

The Examiner has rejected claims 64-91 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In rejecting the claims the Examiner urges that the expression "at the most 1% W/W of free acid" has no support in the originally filed specification and thus constitutes the introduction of new matter. In response to this rejection, Applicant has amended the above noted expression from the claims. The claims presently refer to the monoglyceride component of the adjuvant as having a purity of at least 80%. Support for this limitation is found in the sentence bridging pages 4-5 of the specification.

The Examiner has rejected claims 64-91 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and disctinctly claim the subject matter which Applicant regards as the invention. In rejecting the claims the Examiner notes that the composition includes a monoglyceride preparation having at most 1% W/W of free fatty acid and further recites that the composition further includes a separate fatty acid component. The Examiner urges that it is unclear why the fatty acid is excluded (i.e., limited to at most 1% W/W in one part of the claim and then included in a second part of the claim). The Examiner also urges that the total amount of fatty acid which may be included in the claimed composition should be clearly set forth. In addition, the Examiner notes that the claims should recite specific components and not a vague expression such as "a monoglyceride preparation".

In response to the above rejection under 35 U.S.C. §112, second paragraph, Applicant has amended the claims to more particularly define the invention. In this regard, it is to be noted that component i) is now described as a "monoglyceride", instead of a "monoglyceride preparation". In addition, the phrase "W/W monoglyceride content and at the most 1% W/W of free fatty acid" has been deleted from the claims.

In rejecting claims 64-91 under 35 U.S.C. §112, second paragraph, the Examiner also notes that claim 90 is drawn to a method for enhancing an antibody response to an antigen by administering the adjuvant of claims 64 and 65, but claims 64 and 65 do not recite any antigen. Accordingly, claim 90 has been amended to make it clear that the method is for enhancing an immune response in a human or animal to an antigen administered to the human or animal. Thus, claim 90 is limited to enhancing immune responses in humans or animals to antigens which are administered to that human or animal.

The Examiner has rejected claims 64-76, 78-82 and 84-89 under 35 U.S.C. §102(b) as being anticipated by Isaacs. Applicant has carefully considered this rejection but it is most respectfully traversed for the reasons discussed below.

In order to anticipate a claim, the cited prior art reference must disclose each and every feature of the claimed invention. Applicant submits that Isaacs et al. do not disclose or suggest a composition which contains both monoglycerides and free fatty acids in the amounts required by the claims.

While Isaacs et al. state that "this invention is directed to antiviral and antibacterial activity of fatty acids and monoglycerides, they fail to disclose or

suggest the composition of these two ingredients in the amounts required by Applicant's invention. In fact, Isaacs et al. refer to the antiviral and antibacterial activity of these materials individually, not as components of a composition containing a mixture of fatty acids and monoglycerides in the amount required by Applicant's invention. Thus, Isaacs et al. refers to using fatty acid or monoglyceride as the active component of their invention. In t his regard, it is to be noted that Isaacs et al. state that the active component is "selected from the group consisting of the fatty acids and monoglycerides thereof" and does not mention mixtures of these materials and furthermore, does not mention mixtures of these materials which are contained in the amounts required in Applicant's claims. In this regard, it is to be also noted that the examples (Tables) in Isaacs et al. describe either a fatty acid composition or a monoglyceride composition. There are no examples of a composition comprising both a monoglyceride and a fatty acid composition in the amounts required by Applicant's invention. Furthermore, Isaacs et al. are only concerned with the use of fatty acid or monoglyceride for its antiviral or antibacterial utility. Isaacs et al. do not even remotely disclose or suggest combining these two materials in the amounts required by Applicant's invention to achieve a totally different utility which relates to enhancing the immune response to an antigen.

In view of the above, it is clear that Isaacs et al. do not anticipate Applicant's invention. Accordingly, the rejection of claims 64-76, 78-82 and 84-89 should be withdrawn.

The Examiner has rejected claims 64-91 under 35 U.S.C. §103(a) as being unpatentable over WO 93/06921 by itself in combination with Amselem, Wright, Koga, Carrano individually or in combination. In rejecting the claims, the Examiner notes that WO discloses formulations containing monoglyceride

preparation and observes that the preparation contains 98.8% monoglyceride and 1% free fatty acid. The Examiner acknowledges that WO does not teach the addition of fatty acid in addition to what is already present (i.e. 1%) in the monoglyceride preparation. The Examiner turns to the teaching of Amselem to establish that oleic acid is a useful component for the delivery of vaccine formulations. The Examiner also turns to the teaching of Wright for his teaching of oleic acid as one of the components of an oral vaccine formulation. The Examiner also turns to the teaching of Koga for his teaching of oleic acid as a component in a vaccine formulation and to the teaching of Carrano for his teaching that oleic acid is preferred as a genetic vaccine facilitator. The Examiner concludes from the above that it would be obvious to add oleic acid to the WO formulation with the expectation of obtaining at least an additive effect or the best possible results since the secondary references teach that oleic acid is used in vaccine preparations as an adjuvant. Applicant has carefully considered this rejection but it is most respectfully traversed for the reasons discussed below.

WO 93/06921 discloses particles comprising monoglyceride (98.8% and 1% fatty acid), water and a "fragmentation agent". The adjuvant describedin Applicant's invention does not contain any fragmentation agent. Furthermore, Applicant's adjuvant comprises at least 2% fatty acid, which distinguish it over WO 93/06921, since in this publication the only fatty acid mentioned is the fatty acid inherently present in the monoglyceride, which is at the most 1%.

According to the Examiner, the only thing lacking in WO to arrive at Applicant's invention, is the addition of a fatty acid. According to the Examiner it would be obvious based on the four prior art references mentioned to add oleic acid to the formulation of WO 93/06921.

The four publications (Amselem, Wright, Koga and Carrano) mention the fatty acid oleic acid as one component out of many in a formulation. No monoglyceride are mentioned in these formulations, i.e. there is no indications in any of the four prior references, that the oleic acid mentioned in these could be formulated together with monoglyceride, and there is no teaching in any of the references of an additive effect.

Furthermore, there is no indication in WO 93/06921 that an additional fatty acid should be added besides the amount inherently contained in the monoglyceride. Thus, there appears to be no motivation from this reference to supply or add additional fatty acids to the composition. At best, the four prior art references only suggest that the fatty acid inherent in the formulation of WO 93/06921 could be oleic acid, and not that additional oleic acid should be added to the formulation. Moreover, none of the references teach that the total fatty acid content should exceed 1%, let alone specifically recited ratios.

Amselem describes vaccine compositions that are nanoemulsions of particles having a lipid core and which is surrounded by at least one phospholipid bilayer. In the description is mentioned that the lipid compositions suitable for use as the lipid core of the emulsomes may be triglycerides, ester of monounsaturated fatty acids, monoester of fatty acids, cholesterol and cholesterol esters and that the lipid cores may further comprise antioxidant. It is also mentioned that negatively charged lipid molecules such as oleic acid may be added to the lipid phase of the emulsomes to increase the zeta potential of the composition. The emulsomes further comprises a high content of phospholipids.

The compositions described in Amselem comprises at least 5 different components besides fatty acids. There is no indication in Amselem of fatty acids being an obvious choice to formulate together with monoglycerides. When reading the teaching of WO 93/06921 and Amselem, there are no indications that would lead a person skilled in the art to pick out the monoglyceride component of WO 93/06921 and the fatty acid component of Amselem and combine these.

Wright teaches an oral preparation useful as a vaccine against gram negative bacterial infection. The gist of the invention is the use of a lipid vesicle preparation comprising a masking agent, which disguises the fecal-like smell of the bacteria. The preparation comprises a number of different substances, such as glycerol monostearate, soya steroler, soybean oil, cherry or peppermint oil, polysorbate 60, oleic acid and water. The function of oleic oil is not described. In the Examples is mentioned a composition comprising 0.1 % oleic acid.

The above comments with respect to Amselem also apply to Wright. Oleic acid is only mentioned as one component among many, and its function in the composition is not described. There is no indication in the application that oleic acid are an obvious choice for use together with a monoglyceride.

Furthermore, the concentration of oleic acid in the composition of Wright is only 0.1 % - which is much less than the amount used in Applicant's invention. As Applicant's see it the small amount of oleic acid used does not render it the first, obvious choice to combine with the teaching of WO 93/06921.

Koga describes a vaccine for dental caries. The main aspect of the patent is the preparation of a protein antigen from *Streptococcus mutans*. The patent

describes a vaccine comprising a protein antigen formulated together with carriers, diluents or other additives. As one component among the vast number of additives mentioned is mentioned oleic acid as an adjuvant fat-soluble component.

In Koga oleic acid is only mentioned as one component among many, and there is no indication in the Koga's application that the specific component oleic acid is a suitable choice for use together with monoglyceride in an adjuvant composition.

Carrano describes a method of introducing genetic material into a cell. The genetic material is distributed together with a genetic vaccine facilitater (GVF) agent that are selected from anionic lipids, enzymes, saponins etc. Oleic acid is mentioned as a GVF.

The GVF consists of only one component, i.e. one phase. Furthermore, the genetic material/GVF is not intended for mucosal administration.

Thus, it would not be obvious to combine the teaching of Carrano, that describes a one-component system for non-mucosal use wherein oleic acid/fatty acids are mentioned as one component out of a vast number of components with the teaching of WO 93/06921, since Carrano does not provide any references or indications for doing so.

The Examiner has rejected claims 64-91 under 35 U.S.C. §103(a) as being unpatentable over WO 93/06921 by itself in combination with Amselem, Wright, Koga, Carrano individually or in combination or further in view of Isaacs. In rejecting the claims the Examiner urges that one skilled in the art would be

motivated to add a fatty acid to the formulations of WO since fatty acids are also effective against viruses as taught by Isaacs. Applicant has carefully considered this rejection but it is most respectfully traversed for the reasons discussed below.

Firstly, this rejection is the same as the previously discussed rejection in item 8 on page 5 of the Office Action with the only exception being that the Examiner further includes Isaacs as another secondary reference. In this regard, the Examiner urges that Isaacs teaches the effectiveness of a combination of monoglyceride and a fatty acid against viruses. Applicant has carefully considered this rejection but it is most respectfully traversed for the reasons discussed below.

As noted above, Isaacs only teaches the use of monoglyceride or fatty acid as an effective virucide and, does not disclose the combination of these two ingredients in a vaccine adjuvant, let alone the combination of these two ingredients in the specified amounts required in Applicant's invention. Furthermore, as discussed above, none of these cited references provide the motivation to add oleic acid to the acid inherently found in WO 93/06921. As noted above, WO inherently contains a maximum amount of only 1% free fatty acid. Furthermore, as also noted above, Amselem, Wright, Koga and Carrano at best only suggest that one of the free amino acids found in the 1% inherently contained in WO 93/06921, may be oleic, none of these references disclose or suggest that oleic acid should be added to the free amino acid found in WO 93/06921. Furthermore, as also discussed above, none of the examples of Isaacs et al. contain the combination of monoglyceride and free fatty acid, let alone the combination in the amounts required by Applicant's invention.

Furthermore, as noted in the discussion of Isaacs et al. above, this reference describes a totally different invention since the Isaacs patent concerns a formulation for killing viruses and bacteria, not an adjuvant formulation for administering together with an antigen. Therefore, the fact that fatty acids are also effective against viruses is not important at all for the preparation of an adjuvant composition. Clearly, it would not be obvious for a person skilled in the art to combine the teachings of Isaacs et al. with the other cited references since the technical fields are not related.

In view of the further amendment to the claims and the above arguments, Applicant respectfully requests reconsideration and allowance of all the claims which are currently pending in the application.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

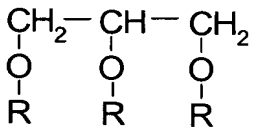
IN THE CLAIMS:

Please cancel claim 64 without prejudice or disclaimer with respect to the subject matter recited therein.

Please amend the below claims as follows:

65(Amended). An adjuvant for use in a vaccine, the adjuvant consisting essentially of

i) a monoglyceride [preparation] having a purity of at least 80% [w/w monoglyceride content and at the most 1% w/w of free fatty acid], the monoglyceride having the formula



wherein R is selected from H and an acyl group containing from 6 to 24 carbon atoms with the proviso that two of the R groups are H, and

ii) a fatty acid with 6 to 24 carbon atoms, the acyl group of the fatty acid being saturated or unsaturated,

i) and ii) being present in the adjuvant in a weight ratio of from 0.1/50 to 50/1 so that the combination of i) and ii) elicits an immune response when administered to an animal.

66(Amended). An adjuvant according to claim [64 or] 65, wherein the vaccine contains an antigen component.

67(Amended). An adjuvant according to claim [64 or] 65, wherein the [content] purity of monoglyceride [in the monoglyceride preparation] i) is at least 90%.

68(Amended). An adjuvant according to claim [64 or] 65, wherein the [content] purity of monoglyceride [in the monoglyceride preparation] i) is at least 95%.

69(Amended). An adjuvant according to claim [64 or] 65, wherein the acyl group of the monoglyceride [in the monoglyceride preparation] i) contains from 8 to 20 carbon atoms.

70(Amended). An adjuvant according to claim [64 or] 65, wherein the acyl group of the monoglyceride [in the monoglyceride preparation] i) contains from 14 to 20 carbon atoms.

71(Amended). An adjuvant according to claim [64 or] 65, wherein the acyl group of the fatty acid ii) contains from 8 to 20 carbon atoms.

72(Amended). An adjuvant according to claim [64 or] 65, wherein the acyl group of the fatty acid ii) contains from 14 to 20 carbon atoms.

73(Amended). A vaccine composition comprising an adjuvant according to claim [64 or] 65, and an immunogenic quantity of an antigen component.

74(Amended). A vaccine or antigen composition according to claim 73, wherein the antigen component is capable of causing the formation of an [antibody] immune response in animals including humans and marine animals.

75(Amended). A vaccine composition according to claim [73] 74, wherein the antigen component is selected from the group consisting of antigens from pathogenic and non-pathogenic bacteria, viruses, parasites and tumor cells.

77(Amended). A vaccine composition according to claim [73] 76, containing, in 100 g of the final composition:

from 0.01 to 90 g of the antigen component
from 1 to 20 g of the monoglyceride [preparation] i)
from 1 to 20 g of the fatty acid ii)
from 0.01 to 99 g of water
from 0.01 to 99 g of PBS or saline

and optionally one or more additional adjuvants or excipients.

78(Amended). A vaccine composition, according to claim [73] 77, wherein the composition comprises additional pharmaceutical excipients selected from the group consisting of preservatives, osmotic pressure controlling agents, pH-controlling agents, organic solvents, enzyme inhibitors, water absorbing polymers, absorption promoters and anti-oxidative agents.

84(Amended). A vaccine composition according to claim 73, wherein the content of monoglyceride [in the monoglyceride preparation] i) of the adjuvant is at least 90%.

85(Amended). A vaccine composition according to claim 73, wherein the content of monoglyceride [in the monoglyceride preparation] i) of the adjuvant is at least 95%.

86(Amended). A vaccine composition according to claim 73, wherein the acyl group of the monoglyceride [in the monoglyceride preparation] i) of the adjuvant contains from 8 to 20 carbon atoms.

87(Amended). A vaccine composition according to claim 73, wherein the acyl group of the monoglyceride [in the monoglyceride preparation] i) of the adjuvant contains from 14 to 20 carbon atoms.

90(Amended). A method of enhancing an [antibody] immune response in a human or animal [including a human] to an antigen administered to said human or animal, the method comprising administering an [antibody] immune

response enhancing effective amount of an adjuvant according to [any of claims 64 or 65] claim 65 to the human or animal.